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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/003,462	12/06/2001	Aillette Mulet Sierra	02451800002	4354

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EXAMINER	
HOLLERAN, ANNE L	

ART UNIT	PAPER NUMBER
1643	

DATE MAILED: 05/02/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/003,462	SIERRA ET AL.	
	Examiner	Art Unit	
	Anne L. Holleran	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 February 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) *14-18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: Notice to Comply

DETAILED ACTION

1. Applicants' amendment filed 2/06/2006 is acknowledged.

2. Claims 1-18 are pending.

Claims 14-18, drawn to non-elected inventions, are withdrawn from consideration.

Claims 1-13 are examined on the merits.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections Withdrawn:

Specification

4. The objection to the specification is withdrawn in view of applicants' remarks pointing out that an amendment to the specification was filed on 5/30/2002.

Claim Objections

5. The objection to the claims is withdrawn in view of applicants' amendment to the dependent claims.

Claim Rejections - 35 USC § 112

6. The rejection of claims 1-13 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of the amendment to the claims.

7. The rejection of claims 1-9, 12 and 13 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for vaccines comprising a TGFα molecule sufficiently characterized by physical or chemical structure, such as by SEQ ID NO, does not reasonably provide enablement for vaccines comprising TGFα molecules identified solely as "self-TGFα", "any derived" self-TGFα, "human TGFα", "TGFα" or "hTGFα" is withdrawn in view of the amendment characterizing TGFα as TGFα that comprises the amino acid sequence of SEQ ID NO: 2.

8. The rejection of claims 1-9, 12 and 13 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn in view of the amendment characterizing TGFα as TGFα that comprises the amino acid sequence of SEQ ID NO: 2.

Claim Rejections - 35 USC § 102

9. The rejection of claims 1, 3, and 13 under 35 U.S.C. 102(b) as being anticipated by Gonzalez (Gonzalez, G. et al., Annals of Oncology, 9: 431-435, 1998) is withdrawn in view of the amendment limiting the scope of the term TGFα.

10. The rejection of claims 1, 3, 12 and 13 under 35 U.S.C. 102(b) as being anticipated by Gonzalez (Gonzalez, G. et al., Vaccine Research, 6(2): 91-100, 1997) is withdrawn is withdrawn in view of the amendment limiting the scope of the term TGFα.

Claim Rejections Maintained:

11. Claims 1 and 2 remain rejected under 35 U.S.C. 102(b) as being anticipated by either Heimbrook (Heimbrook, D.C. et al., Proc. Natl. Acad. Sci., USA, 87: 4697-4701, 1990) or Kunwar (Kunwar, S. et al., J. Neurosurg., 79: 569-576, 1993) as evidenced by Chaudhary (Chaudhary, V.K. et al. Proc. Natl. Acad. Sci., USA, 84, pp4538-4542, 1987). The rejection is maintained for the reasons of record. The original rejection is repeated below:

Claims 1 and 2 are interpreted broadly to include compositions comprising a fusion protein or conjugate of TGFα and a carrier protein with an intended use as a vaccine.

Heimbrook teaches a fusion protein of human TGFα and PE40 (40kDa segment of the Pseudomonas exotoxin A protein) in combination with phosphate buffered saline (interpreted to be within the scope of an "adjuvant") (see 4698, 1st –2nd column and 4699, 1st-2nd column).

Kunwar also teaches a fusion protein of human TGFα and PE40 (see Chaudhary for evidence that Kunwer's TGFα is human TGFα, page 4538, 2nd column). Kunwer teaches the fusion protein in combination with human serum albumin (interpreted to within the scope of an "adjuvant", see page 570, 2nd column, "Recombinant Proteins"). Kunwer also teaches that the fusion protein construct is immunogenic (see page 574, 2nd column). Therefore, Kunwar teaches a fusion protein that is the same as that claimed. Therefore, either Heimbrook or Kunwar teaches a composition that is the same as that claimed.

Applicants did not specifically argue the merits of this rejection except to state that none of the cited references teach TGFα that comprises the amino acid sequence of SEQ ID NO: 2. This argument is not found persuasive because the amino acid sequence of SEQ ID NO: 2 appears to be the sequence of human TGFα, and both of the above cited references teach human TGFα. Therefore, the rejection is maintained.

Double Patenting

12. The provisional rejection of claims 1-13 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 7, 10, 11, 12, 23, and 26 of copending Application No. 10/005,341 is maintained for the reasons of record. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of copending application 10/005,341 appear to claim compositions that fall within the scope of the vaccine compositions comprising conjugates or fusion proteins of TGFα and a carrier protein.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicants' remarks concerning holding this rejection in abeyance until allowable subject matter is identified is acknowledged.

New Grounds of Rejection:

13. Claims 1, 2, 4, 5, and 7-11 are objected to because of the use of the term TGFα instead of human TGFα or hTGFα. SEQ ID NO: 2 appears to be the amino acid sequence of human

TGFα. The phrase "human TGFα" should appear in the first claim, followed by the abbreviation "hTGFα" in parentheses, and the subsequent claims should then use the term "hTGFα".

14. The specification is objected to for not being in compliance with the sequence rules. Figure 1 contains sequences that are not identified by sequence identifier either in the figure itself or in the description of the drawings. Applicants may amend either the drawings or the specification (in the description of the drawings) to include the sequence identifiers of the two sequences.

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

APPLICANT IS GIVEN THE RESPONSE PERIOD OF THIS OFFICE ACTION WITHIN WHICH TO COMPLY WITH THE SEQUENCE RULES, 37 CFR 1.821 - 1.825. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 CFR 1.821(g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136. In no case may an applicant extend the period for response beyond the six-month statutory period. Applicant is requested to return a copy of the attached Notice to Comply with the response.

15. Claims 10 and 11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for vaccines comprising an EGF molecule sufficiently characterized by physical or chemical structure, such as by SEQ ID NO, does not reasonably provide enablement for vaccines comprising EGF molecules identified solely as EGF. The

specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification generally teaches that the purpose of the claimed vaccines is to treat epithelial tumors dependent on TGFα or TGFα/EGF, or in the treatment of any disease associated with TGFα such as psoriasis (page 2, lines 44-46). Therefore, it appears that the function of the claimed vaccines is to cause the production of antibodies that would interfere with the biological function of TGFα or TGFα/EGF. However, because of the scope of the terms "EGF", as defined in the specification, in comparison with the narrow scope of the working examples provided, it appears that the specification fails to enable the full scope of the claimed vaccines.

Factors to be considered in determining whether undue experimentation would be required to practice the full scope of the claimed inventions are: 1) quantity of experimentation necessary; 2) the amount of direction or guidance presented in the specification; 3) the presence or absence of working examples; 4) the nature of the invention; 5) the state of the prior art; 6) the relative skill of those in the art; 7) the predictability or unpredictability of the art; and 8) the breadth of the claims. See In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

The specification defines the scope of the term EGF as including any fragment derived of EGF that has the same immunology properties and/or similar effects to the original molecule; the specification further includes original substitutions of amino acids, change of specific amino acids that increase the stability and/or activity, chemical modifications, and other changes to structure (page 7, paragraph 42). Therefore, the claimed vaccines read on compositions comprising protein molecules that include variants of EGF, such variants including, for example,

deletions from, or insertions or substitutions of residues within EGF. Because of the definition of the terms provided by the specification, the genus of molecules encompassed by the claimed vaccines is large. Furthermore, the study of the relationship between the primary amino acid sequence and protein function is highly unpredictable. Bowie et al (Science, 247: 1306-1310, 1990) teaches that while it is known that many amino acid substitutions are possible in any given protein, the position with the protein sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Burgess et al (J. Cell Biology, 111: 2129-2138, 1990) teaches that replacement of a single lysine residue at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein. Lazar et al (Molecular and Cellular Biology, 8: 1247-1252, 1988) teaches that replacement of aspartic acid at position 47 with alanine or asparagines does not affect biological activity while replacement with serine or glutamic acid sharply reduces the biological activity of the protein. These references demonstrate that even a single amino acid substitution will often dramatically affect the biological activity and characteristics of a protein. Given that small changes in protein structure may result in large changes to protein structure and function, the claimed vaccines appear to encompass fusion proteins or conjugates that would, if administered to a subject, result in the formation of antibodies that will not bind to a full-length EGF protein, and therefore, the usefulness of the vaccines, as currently claimed, cannot be determined without further experimentation.

This further experimentation appears to be undue experimentation because of the unpredictability of the protein arts, and because the skilled artisan cannot make and use the broad

genus of "EGF" containing vaccines recited in the claims because such a genus encompasses an unlimited and thereby infinite plurality of amino acid substitutions, deletions, additions, or combinations thereof, as compared with the working embodiments. The disclosure does not adequately describe, provide guidance or give examples of the critical amino acid residues that bestow upon "EGF" the desired characteristics useful for treatment of epithelial cancer or psoriasis by immunotherapy.

16. Claims 10 and 11 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The basis for this rejection is that the specification fails to provide an adequate description of "EGF". This rejection is based on the interpretation of the terms "EGF" encompassing a genus of molecules that are not adequately described by the specification.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is for purposes of the 'written description' inquiry, *"whatever is now claimed"* (see page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is now claimed." (See Vas-Cath at page 1116.)

The claimed vaccines are drawn to compositions comprising fusion proteins or conjugates of "EGF" with a carrier protein. The specification defines the scope of the term

"EGF" as including any fragment derived of EGF that has the same immunology properties and/or similar effects to the original molecule; the specification further includes original substitutions of amino acids, change of specific amino acids that increase the stability and/or activity, chemical modifications, and other changes to structure (page 7, paragraph 42). Therefore, the claimed vaccines read on compositions comprising protein molecules that include variants of EGF, such variants including, for example, deletions from, or insertions or substitutions of residues within EGF. Because of the definition of the terms provided by the specification, the genus of molecules encompassed by the claimed vaccines is large.

The skilled artisan cannot envision the detailed chemical structure of a representative number of molecules encompassed by the term "EGF", because the specification fails to provide a description of a representative number of molecules within each genus encompassed by this term. This is because the definition appears to include almost any modification to the structure of EGF, making each genus very large and encompassing structures of wide variation. Furthermore, the specification has failed to provide a nexus between structure and function, with which one of skill in the art may define each genus.

Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for making or testing it. One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481, 1483. In Fiddes v. Baird, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. 112, is severable from its enablement provision. (See page 1115).

17. Claims 1, and 2 are rejected under 35 U.S.C. 102(b) as being anticipated by Hoeprich (Hoeprich, Jr., P.D. et al., The Journal of Biological Chemistry, 254(32): 19086-19091, 1989).

Hoeprich teaches a conjugate of human TGFα and keyhole limpet hemocyanine, coupled using gluteraldehyde (see page 19087, 1st column). The TGFα was either chemically synthesized or recombinantly synthesized (see Figure 2 on page 19088 and page 19087, 1st column). The resulting conjugate was immunogenic (see Figure 2, and page 19088, 1st column). The adjuvant used was Freund's complete adjuvant (see page 19087, 2nd column). Thus, Hoeprich teaches vaccine compositions that are same as that claimed.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne Holleran, whose telephone number is (571) 272-0833. The examiner can normally be reached on Monday through Friday from 9:30 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached on (571) 272-0832. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Official Fax number for Group 1600 is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

Anne L. Holleran
Patent Examiner
April 30, 2006

LARRY R. HELMS, PH.D.
SUPERVISORY PATENT EXAMINER

Application No.: 10/003,462

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

X 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to these regulations, published at 1114 OG 29, May 15, 1990 and at 55 FR 8230, May 1, 1990.

___ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

___ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

___ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

___ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

___ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

X 7. Other: *contains sequences in the specification that are not identified by sequence identifier*

Applicant Must Provide:

___ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

___ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.

___ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

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